## REMARKS

This is in response to the Office Action mailed July 29, 2009. Applicants herewith petition for a one month extension of time. Claims 1-21 are pending in the application. Claims 1-12, 15 and 16 are withdrawn from consideration. With entry of this Amendment, claims 13 and 14 and 17-21 will be pending for consideration.

### I. Miscellaneous

Applicants thank Examiner Arnold for the courtesy of a telephonic interview on November 3, 2009.

In the Office Action, the Examiner has suggested applicants change the title. In response, applicants have replaced the title with "Stabilized Pravastatin Sodium Polymorph Compositions", which is in line with the amendment to the claims.

The Examiner has noted a misspelling of pravastatin in claim 21. Claim 21, as amended, now recites "pravastatin."

The Examiner acknowledges receipt of applicants' claim of priority under 35 USC § 119.

The Examiner has not acknowledged receipt of applicants' Correction of Inventorship, which was filed July 10, 2009. Applicants respectfully request favorable consideration of the request for corrected inventorship.

### II. Rejection under 35 USC § 112

The Examiner has rejected claim 21, stating that the recitation of the ratio of pravastatin sodium to microcrystalline cellulose is "greater than 2" is new matter. In order

to expedite prosecution, applicants have amended claim 21 to recite "at least 2", which is language explicitly found in paragraph [0021]. Withdrawal of this rejection is respectfully requested.

The Examiner also rejects claims 14 and 17-21 as allegedly being indefinite. In response, applicants have deleted the word "significantly". Withdrawal of this rejection is therefore respectfully requested.

The Examiner also rejects claim 21 for allegedly lacking an antecedent basis for "prevastatin sodium" [sic] in line 2. Applicants respond that this rejection is rendered moot with the amendment to claim 21.

In view of the amendment and above explanations, applicants respectfully request that all rejections under 35 USC § 112 be withdrawn.

### III. Rejections under 35 USC § 102

The Examiner rejects claims 13 and 20 under 35 USC § 102(b) as being anticipated by Dempski (US Patent No. 4173626).

Applicants respectfully traverse this rejection. Claim 13 has been amended to replace "active pharmaceutical ingredient" with "pravastatin sodium". Dempski does not disclose pravastatin sodium. Claim 20 depends from claim 13. In view of this amendment and argument, applicants respectfully request the Examiner to withdraw this rejection.

## IV. Rejection under 35 USC § 103

The Examiner has rejected claims 13 and 14 and 17-21 under 35 USC § 103 over Pflaum (US Patent No. 6740775) in view of Kofler (US Patent No. 6511972). According to the Examiner, Pflaum teaches a process of preparing the sodium salt of pravastatin using open language (claim 6) and Kofler teaches using microcrystalline cellulose, such as Avicel PH 112 having a particle size from 20 to 100 microns for capsule and tablet formulations (column 2, lines 10-15). The Examiner states that the difference between the instant application and Pflaum is that Pflaum does not expressly teach adding microcrystalline cellulose that has an average particle size of from 10 to 200 microns and a weight ratio of pravastatin to microcrystalline cellulose of greater than 1. Kofler is cited to cure this deficiency. Applicants respectfully traverse this rejection.

During the telephonic interview, Examiner Arnold explained that in his opinion, Pflaum is the closest prior art because applicants refer to it in their application. Examiner Arnold suggested applicants submit comparative data showing the superior stability of the claimed pharmaceutical formulation, relative to Pflaum. Applicants have considered the Examiner's suggestion but do not agree that Pflaum is relevant to obviousness. Applicants base this assertion on the fact that Pflaum is concerned with pravastatin sodium per se but not with any particular formulation of pravastatin sodium. Applicants discovered that when pravastatin sodium is wet granulated with an alcohol in admixture with microcrystalline cellulose, the stability of a pravastatin sodium polymorph is adversely affected. Applicants then discovered the solution to this problem and the solution is the claimed invention, which is a specific formulation made in a specific way.

The Examiner relies upon claim 6 of Pflaum. In response, applicants point out that the process of claim 6 does not suggest the process recited in claim 13 or 14 and although the language of claim 6 is "opened ended," Pflaum's specification does not describe or suggest the process recited in claim 13 or 14. Namely, Pflaum does not describe or suggest using wet granulation or a wet phase, comprising pravastatin sodium, microcrystalline cellulose and liquid, wherein a weight ratio of pravastatin sodium to microcrystalline cellulose is greater than 1.0 and/or the weight ratio of pravastatin sodium liquid is greater than 1.0. Thus, even if claim 6 of Pflaum could be interpreted as including other steps or ingredients, one of skill in the art would not have been directed by this claim or the specification to the process by which the compositions of the present invention were obtainable. For instance, at column 4, lines 26-52, Pflaum describes a process but is silent with regard to the features recited in claim 13 or 14. In the present invention, the ratio of the amount of liquid used to the amount of active ingredient is relevant and not a matter of routine optimization. The examples of the present application show that the amount of liquid used for granulation can affect the stability of the active pharmaceutical ingredient.

Kofler does not cure these deficiencies. Kofler discloses a dry formulation adapted for reconstitution with water comprising amoxicillin trihydrate and potassium clavulanate active ingredients, and microcrystalline cellulose filler, wherein said filler comprises at least 20 % of the weight of the dry formulation. Applicants do not dispute that microcrystalline cellulose was a known pharmaceutical filler at the time of the invention. However, Kofler teaches nothing that would cure the main deficiencies of Pflaum, as outlined above. Thus, even if there had been a motivation to combine the art as the Examiner has done, one of

skill in the art could not have arrived at the present invention by combining Kofler with Pflaum. The fact that Kofler teaches Avicel PH 112 having a particle size from 20 to 100 microns for capsule and tablet formulations does not alter this conclusion.

The Examiner also has rejected claims 13, 14 and 17-21 under 35 USC § 103 as being obvious over Keri (WO 01/43723) in view of Kofler. According to the Examiner, Keri teaches novel forms of pravastatin sodium and methods of making and using pravastatin sodium. The Examiner acknowledges that Keri does not explicitly disclose the limitations recited in claims 14 and 17. The Examiner states that the difference between the instant application and Keri is that Keri does not expressly teach adding microcrystalline cellulose that has an average particle size of from 10 to 200 microns and a weight ratio of pravastatin to microcrystalline cellulose of greater than 1. Kofler is again cited for disclosing microcrystalline cellulose having a particle size from 20 to 100 microns for use in capsule and tablet formulations.

The Examiner also discounts the method by which the compositions of the present invention were made and shifts the burden to applicants to show non-obvious differences resulting from the recited process.

Applicants respectfully traverse this rejection. In further response, applicants explain that the instant invention can be distinguished over the cited prior art in at least three ways. First, the instant invention involves the use of the wet granulation process comprising microcrystalline cellulose and a liquid. Secondly, the ratio of active pharmaceutical ingredient to microcrystalline cellulose or the liquid is predetermined. That ratio should be above 1. Thirdly, the predetermined ratios do not prevent the end

composition from containing more microcrystalline cellulose than the pravastatin sodium, as the ratio must only be observed during the wet granulation phase ("at least the wet granulation phase"). After this has been done, more filler, such as microcrystalline cellulose, can be added. The resultant pharmaceutical composition is stabilized.

Keri is not concerned with stabilizing a pharmaceutical composition. It teaches a variety of pravastatin sodium polymorphs (A-L) and explains that a particular crystalline form of a compound is highly dependent upon exacting control of conditions and that those conditions include pH, the solvent, the temperature profile, the form of crystals that are added. It mentions the importance of selecting the proper protic and aprotic solvents and cooling systems. All of these teaching are toward making particular polymorphs and not a formulation for stabilizing a polymorph *i.e.* preventing the conversion of one polymorph into another. Keri's teachings are not directed to making particular formulations of a polymorph. Keri teaches general methods for tabletting an active ingredient. It nowhere directs the skilled artisan toward the above-described process, which is recited in claims 13 and 14. In fact, Keri, like Pflaum, does not disclose any particular formulation. It doesn't disclose applying a wet granulation step comprising microcrystalline cellulose and liquid in specific ratios for preparing a pharmaceutical composition. It does not disclose a composition that would be inherently stabilized due to this wet granulation step.

One of skill in the art reading Keri alone or in combination with Kofler, would not have deduced that the composition and the ratios are important in the wet granulation phase for producing a stabilized pharmaceutical composition, wherein the polymorph of the active ingredient does not interconvert to another polymorph over time. One reading about

general methods for tabletting pravastatin would not know how to stabilize the final product. Certainly, the skilled artisan would not have arrived at the present invention just by following the teachings of Keri with Kofler.

Applicants again argue that the specific ingredients and the weight ratios of those ingredients, as recited in claim 13, are relevant to the stability of the final product. That is, a comparison of the results of Examples 12-15, 17 with the results in Examples 1, 5, 6, 9, 16 clearly shows that the weight ratio of pravastatin sodium to microcrystalline cellulose greater than 1.0 and/or the weight ratio of pravastatin sodium to liquid greater than 1.0 yield surprising and advantageous effect of stabilizing the pravastatin sodium into a single polymorph during wet granulation.

Because Keri lacks specifics with regard to formulation techniques, one reading Keri would not have been motivated to stabilize a composition comprising pravastatin sodium inhibitor, specifically pravastatin sodium and microcrystalline cellulose, by taking advantage of the wet phase step comprising pravastatin sodium, specifically pravastatin sodium, microcrystalline cellulose and liquid, wherein a weight ratio of pravastatin sodium to microcrystalline cellulose is greater than 1.0 and/or the weight ratio of pravastatin sodium to liquid is greater than 1.0.

In view of the above arguments and amendment, applicants respectfully request the Examiner to reconsider and withdraw the rejection over Keri combined with Kofler.

## V. Double Patenting Rejection

The Examiner has rejected claims 13, 14 and 17-21 for obviousness-type double patenting over claims 1, 7, 14, 17, 18, 19, 25, 32, 33 and 39 of Kerc (US Patent No. 6,680,341) in view of Pflaum (US Patent No. 6740775) and Kofler. Applicants respectfully traverse this rejection. Kerc teaches stabilization by use of a buffer (claims 1, 7, 32, 33) or by pH (claims 14, 17, 18, 19, 25). Furthermore, Kerc discloses a ratio of active ingredient to microcrystalline cellulose that is always below 1. Although the recited claims are directed to stabilized formulations, the methods of stabilization are different from what is claimed. Nothing in claims 1, 7, 14, 17, 18, 19, 25, 32, 33 and 39 of Kerc would direct the skilled artisan to the claimed invention and one could not arrive at the claimed invention by combining the teachings of Pflaum '775 and Kofler, for reasons discussed above. Accordingly, applicants respectfully request the Examiner to reconsider and withdraw this rejection.

The Examiner also rejects claims 13, 14 and 17-21 for obviousness-type double patenting over claims 1, 12, 13 and 17 of Pflaum (US Patent No. 6,531,507) in view of Pflaum (US Patent No. 6,740,775) and Kofler. Applicants respectfully traverse this rejection. Claims 1, 12, 13 and 17 of Pflaum '507 solve the problem of stabilizing the composition by using buffering substance or basifying substance. This is different from what applicants claim. The deficiencies of Pflaum '775 and Kofler have been discussed above and are applicable to the non-obviousness of the claims in view of Pflaum '507.

In these obviousness-type double patenting rejections, the Examiner continues to discount the relevance of the process by which the claimed invention is made. However,

applicants again direct the Examiner's attention to the Examples in the specification wherein the weight ratio of the pravastatin sodium to microcrystalline cellulose is greater than 1.0 and/or the weight ratio of pravastatin sodium to liquid greater than 1.0 are shown to yield the surprising and advantageous effect of stabilizing the pravastatin sodium into a single polymorph during wet granulation. In view of these results, applicants respectfully request the Examiner to give weight to the process by which the claimed compositions were made and to withdraw the obviousness rejections over the cited claims and prior art, accordingly.

## CONCLUSION

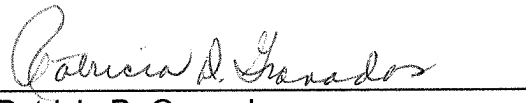
Applicants again thank Examiner Arnold for the courtesy of an interview. In view of the above amendment and arguments, applicants respectfully request the Examiner to withdraw all rejections and issue a Notice of Allowance. Should the Examiner believe that anything further is necessary in order to place this application in better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below.

In the event that additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefore are hereby authorized to be charged to our Deposit Account No. 01-2300 referencing Atty. Docket No. 029489-00023.

In the event that any fees are due with respect to this paper, please charge Deposit Account No. 01-2300, referencing Atty. Docket No. 029489.00023.

Dated: November 23, 2009

Respectfully submitted,

By 
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